# Thrombotic Thrombocytopenic Purpura: Incidence of Congenital Form of Disease in North Moravia (Region Moravia-Silesia)

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**Abstract:** Thrombotic thrombocytopenic purpura (TTP) was first described by Eli Moschcowitz in 1924. The pathophysiology of this disease is related to unusual, large multimers of von Willebrand factor in microcirculation, that are insufficiently cleaved by ADAMTS13 protease (a disintegrin-like and metalloprotease with thrombospondin type 1motif,13). Congenital TTP/Upshaw-Schulman syndrome is less frequent than acquired one TTP/HUS (haemolytic-ureamic syndrome).

Short characteristic of patients with inherited form of TTP is reported as well as their clinical and laboratory features and management of treatment.

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## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystem disorder, often characterized by a pentad of clinical features: microangiopathic haemolytic anaemia, fever, thrombocytopenia, renal and neurological abnormalities [1]. Platelet-rich microvascular thrombi induce renal and cerebral lesions. Pathophysiology of TTP is caused by the lack of functioning of von Willebrand cleaving metalloprotease. Untreated TTP is almost always fatal, however the mortality is reduced approximately to 25% by therapeutic plasmapheresis [2, 3].

### *ADAMTS13*

A disintegrin-like metalloprotease with thrombospondin type 1 repeats13 is one of the 19 ADAMTS proteases. ADAMTS13 is responsible for the proteolytic degradation of von Willebrand factors (vWF) multimers that are produced by vascular endothelial cells. ADAMTS13 gene is located on chromosome 9q34, includes 29 exons and spans approximately 37 kB [4]. ADAMTS13 specifically cleaves a peptidyl bond between Tyr1605 and Met1606 in the A2 domain of vWF molecule [5]. Several mutations of this gene all over its length are known. The most frequent causative mutation that decreases cleaving protease activity is mutation in exon 29 [6, 7], the other common mutations can be found in exon 13 and 21 [8]. Acquired deficiency occurs with the production of autoantibodies inhibiting ADAMTS13 activity [4].

### *Congenital and acquired TTP (TTP-HUS like syndrome)*

In 1960 Schulman et al. and in 1978 Upshaw reported first cases of congenital TTP, later known as Upshaw-Schulman syndrome [9, 10]. However, hereditary form of disorder is very rare [11, 12]. TTP can occur in neonates (as a newborn icterus), with later onset of clinical symptoms and laboratory findings such as thrombocytopenia, microangiopathic haemolytic anaemia (MAHA with schistocytes on the blood smear) elevated serum lactate dehydrogenase (LDH), and renal dysfunction (micro and macro hematuria).

But TTP is rarely diagnosed in young children. Much more common is the clinically and pathologically similar disorder haemolytic-ureamic syndrome (HUS) [4]. A typical HUS is preceded by diarrhoea (D+HUS) and atypical HUS occurs with no diarrhoea prodrome (D-HUS) [13]. D+HUS is the most common form and is caused by Shiga-toxin producing bacteria predominantly Escherichia coli. HUS almost never recurs but 30 to 40% of patients with TTP suffer relapse. It is now known that TTP but not HUS has a severe deficiency in ADAMTS13 [14]. TTP (-HUS like syndrome) is associated with cancer, pregnancy and postpartum state, autoimmune disorders, infection etc. A large percentage of cases of acquired idiopathic TTP, which is difficult to recognize and diagnose clinically, are due to autoantibody formation [15].

## Patients and Methods

One group of 7 patients (Table 1) with congenital form of TTP lives in surroundings of Ostrava. In all patients disease first occurs as a newborn icterus, in one patient (no. 4) disease relapsed in gravidity.

In most patients was detected mutation in exon 29 ins413A; (patients nos. 1, 2, 3 and 5), in 2 patients (nos. 6 and 7) were found mutations in exon 29/exon 13, in patient no. 4 was detected mutation in exon 13 only. All patients show reduced plasma level of ADAMTS13, which correlates with congenital TTP. The management of patients' treatment consists of therapeutic plasma exchange (TPE) in regular intervals (Table 1) that are arranged empirical. During each plasmapheresis is treated 1.5 of plasma volume. Apheretic procedures are performed on separators COMTEC (Fresenius HemoCare, GmbH, Germany) via peripheral venous access. In spite of it there occurs random relapses in the course of time; trigger events represent infections or concomitant disease

**Table 1 – Clinical and laboratory findings in patients with congenital TTP**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Age (years) | 31 | 33 | 23 | 38 | 32 | 15 | 13 |
| Sex | M | M | M | F | F | F | F |
| Height (cm) | 178 | 178 | 186 | 158 | 165 | 158 | 155 |
| Weight (kg) | 128 | 108 | 80 | 57 | 83 | 51 | 46 |
| Blood group | B | B | B | 0 | B | B | B |
| Frequency of TPE | 3 weeks | 7 weeks | 6 weeks | irregular | 3 weeks | no | no |
| FFP infusion | no | no | no | no | no | yes 10 ml/kg | yes 10 ml/kg |
| Plasma volume replacement | 1.5 PV | 1.5 PV | 1.5 PV | 1.5 PV | 1.5 PV | no | no |
| Improving after TPE | yes | yes | yes | yes | yes | no | no |
| Platelet count $\times 10^9$ */** | 86/302 | 70/340 | 140/280 | 52/350 | 30/240 | 57/240 | 60/220 |
| Renal symptoms | MIA, MAU | renal insufficiency | MIA, MAU | MIA, MAU | MIA, MAU | no | no |
| Neurological symptoms | no | yes | no | no | yes | no | no |
| ADAMTS13 | 2% | 3% | 2% | 1.5% | 3% | <3% | <3% |
| Inhibitor | no | no | no | no | yes$^+$ | no | no |
| Genetical findings | InsA4143 ex29/InsA4 143ex29 | InsA4143 ex29/ex29 | InsA4143 ex29/InsA4 143ex29 | ex13/ | InsA4143 ex29/ex22 | InsA4143 ex29/ex13 | InsA4143 ex29/ex13 |

PV – plasma volume; TPE – therapeutic plasma exchange; MIA – micro hematuria; MAU – macro hematuria;*platelets count during relapse; **platelets count after PF; FFP – fresh frozen plasma; $^+$inhibitor appeared after PF

(thyreotoxicosis in patient no. 4). Two patients – teenage sisters (patients nos. 6 and 7) are treated regularly with quarantine fresh frozen plasma (FFP) infusions (10 ml/kg). One patient (no. 5) acquired ADAMTS13 inhibitor after plasmapheresis.

The therapeutic plasmapheresis in patients is effective if it achieves clinical and laboratory remission (platelet count recovery and LDH level normalization).

**Discussion**

In Moravia-Silesia region can be found considerable group of patients with inherited TTP, with suggesting incidence 0.37/100.000/year [15]. The patients regularly undergo therapeutic plasmapheresis exchange (TPE) with exchange of 1.5 of plasmatic volume, with satisfactory laboratory and clinical respond without further progress of clinical complications (except of patient no. 5). Plasma exchange with quarantine fresh frozen plasma is a first-line treatment for TTP [14, 16]. The preference of PE (plasma exchange) over plasma infusion was demonstrated in clinical trial conducted by the Canadian Apheresis group in 1991 [17]. In the special issue of Journal of Clinical Apheresis (Journal of American Society for Apheresis) from 2007 as well as in the previous issue (2000) is plasma exchange for TTP patients submitted into the category I that means standard and acceptable therapy [13]. PE allows to supply failing ADAMTS13 metalloprotease, to remove pathogenic substances including large uncleaved von Willebrand factors (vWF) multimers and as well allows to treat large volumes of plasma [18, 19]. However in teenage patients are preferred quarantine FFP infusions due to poor toleration of TPE procedures. Complications of plasma exchange treatment for TTP represent primarily allergic reactions (mild or severe) and those related to status of peripheral venous system.

**Conclusion**

Congenital TTP is rare life-threatening condition. Acquired TTP is idiopathic secondary complications of autoimmune disease, malignancy, pregnancy, certain drugs, or infection. TTP survival rate and prognosis are poor without plasma treatment. In hereditary TTP regular therapeutic plasmapheresis is indicated, in secondary form platelet count recovery can be achieved after repeated plasma exchange.

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## References


1. MOSCHCOWITZ E.: Hyaline thrombosis of the terminal arterioles and capillaries: A hitherto undescribed disease. *Proc. N. Y. Pathol. Soc.* 24: 21–24, 1924.
2. AMOROSI E. L., ULTMANN J. E.: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. *Medicine* 45: 139–159, 1966.
3. LÄMMLE B., KREMER HOVINGA J. A., ALBERTO L.: Thrombotic thrombocytopenic purpura. *J. Thromb. Haemost.* 3: 1663–1675, 2005.
4. GEORGE J. N., SADLER J. E., LÄMMLE B.: Platelets: thrombotic thrombocytopenic purpura. *Hematology Am. Soc. Hematol. Educ. Program Book* 2002: 315–334, 2002.
5. DENT J. A., BERKOWITZ S. D., WARE A., KASPER C. K., RUGGETI Z. M.: Identification of cleavage site directing in immunochemical detection of molecular abnormalities in type IIA von Willebrand factor. *Proc. Natl. Acad. Sci. USA* 87: 6303–6310, 1990.
6. SCHNEPPENHEIM R., BUDDE U., OYEN F., ANGERHAUS D., AUMANN V., DREWKE E., HASSENPFLUG W., HÄBERLE J., KENTOUCHE K., KOHNE E., KURNIK K., MUELLER-WIEFEL D., OBSER T., SANTER R., SYKORA K. W.: Von Willebrand cleaving protease and ADAMTS13 mutation in childhood TTP. *Blood* 101: 1845–1850, 2003.
7. HRACHOVINOVÁ I., RITTICH Š., SALAJ P., SUTTNAR J., DYR J. E., ŠULÁKOVÁ T., PTÁK J., ĎULÍČEK P., SEEMAN T.: Vrozená forma trombotické trombocytopenické purpury (in Czech). *Čas. Lék. čes.* 145: 390–392, 2006.
8. LEVY G. G., NICHOLS W. C., LIAN E. C., FOROUD T., MCCLINTICK J. N., MCGEE B. M., YANG A. Y., SIEMIENIAK D. R., STARK K. R., GRUPPO R., SARODE R., SHURIN S. B., CHANDRASEKARAN V., STABLER S. P., SABIO H., BOUHASSIRA E. E., UPSHAW J. D. JR., GINSBURD D., TSAI H. M.: Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 413: 488–494, 2001.
9. KOKAME K., AOYAMA Y., MATSUMOTO M., FUJIMURA Y., MIYATA T.: Inherited and de novo mutation of ADAMTS in patient with Upshaw-Schulman syndrome. *J. Thromb. Haemost.* 6: 213–215, 2008.
10. SCHULMAN I., PIERCE M., LUKENS A., CURRIMBHOY Z.: Studies on thrombopoesis, I: a factor in normal human plasma required for platelet production; chronic thrombocytopenia due its deficiency. *Blood* 16: 943–957, 1960.
11. FURLAN M., ROBLES R., SOLENTHALER M., WASSMER M., SANDOZ P., LÄMMLE B.: Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. *Blood* 89: 3097–3103, 1973.
12. VESELY S. K., GEORGE J. N., LÄMMLE B.: ADAMTS13 activity in thrombotic thrombocytopenic purpura – hemolytic uremic syndrome: relation to presenting features and clinical outcome in a prospective cohort of 142 patients. *Blood* 102: 60–68, 2003.
13. SZCZEPIORKOWSKI Z. M., SHAZ B. H., BANDARENKO N., WINTERS J. L.: The new approach to assignment of ASFA categories – Introduction to the fourth special issue: Clinical applications of therapeutic apheresis. *J. Clin. Apher.* 22: 96–105, 2007.
14. GEORGE J. N.: Congenital thrombotic thrombocytopenic purpura: Lessons for recognition and management of rare syndromes, commentary on Peters et al. *Pediatr. Blood Cancer* 50: 947–948, 2008.
15. MANNUCCCI P. M., PEYVANDI F.: TTP and ADAMTS13: when is testing appropriate? *Hematology* 2007(1): 121–126, 2007.

16. FURLAN M., LÄMMLE B.: Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor – cleaving protease. *Best Pract. Res. Clin. Haematol*. 14: 437–454, 2001.
17. ROCK G. A., SHUMAK K. H., BUSKARD N. A., BLANCHETTE V. S., KELTON J. G., NAIR R. C., SPASOFF R. A.: Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N. Eng. J. Med*. 325: 393–397, 1991.
18. PEREIRA A.: Efficacy of different plasma sources in the treatment of thrombotic thrombocytopenic purpura. *Vox Sang*. 4: 111–117, 2009.
19. BRUNSKILL S. J., TUSOLD A., BENJAMIN S., STANWORTH S. J., MURPHY M. F.: A systematic review of randomized controlled trials for plasma exchange of thrombotic thrombocytopenic purpura. *Transfus. Med*. 17: 17–35, 2007.